REMARKS

1. Sequence Listing

The Examiner has objected to the Specification for failing to disclose SEQ ID Nos for the amino acid sequence disclosed on page 43, lines 2 and 3. Applicant would like to direct the Examiner's attention to MPEP 2421.02 et seq. which requires applicants to list all amino acid sequences of 4 or more amino acids residues and all unbranched nucleotide sequences with 10 or more bases in a sequence listing. In the instant case, the two nucleotide sequences identified by the Examiner on page 43 of the Specification only consist of 8 nucleotide bases. Therefore, Applicant is not required to list these nucleotide sequences in their Sequence Listing. Accordingly, Applicant has not prepared a Supplemental Sequence Listing with these sequences. Reconsideration and removal of the objection is respectfully requested.

2. Restriction Requirement

The Examiner has maintained the full scope of the Restriction Requirement and has withdrawn claims 8, 12-15, 18, 24-28 and 30-52 as being drawn to non-elected species or inventions. Applicant reconfirms their election of the claims of Group 1 and the species elections set forth in Paper Nos. 9, 12 and 15. Applicant has cancelled claims 24-28 and 30-52 as being drawn to a non-elected invention (Groups 2-94) without prejudice or disclaimer of the subject matter contained therein and reserves their right to pursue these claims in a divisional application. Applicant has withdrawn claims 8, 12-15 and 18 directed to the non-elected species of elected group 1 with the understanding that the scope of the search and examination will be broadened in the event that the elected species is found patentable.

3. Priority Claim

The Examiner has recognized Applicant's claim for foreign priority under 35 U.S.C. §119(b) but notes that a certified copy of this document has not yet been filed. Applicant is in

the process of obtaining a certified copy of this document and will file it with the USPTO when it is received.

4. Claims

Claim17 has been cancelled. Claim 1 has been amended to incorporate limitations from claims 2, 3, and 17. New claims 58-64 have been added and contain subject matter removed from claims 1, 10, 11, 16, 21, and 29. No new matter has been added.

5. Specification

The Examiner has objected to the Specification because it lacks a specific reference to the prior application(s) it claims benefit from in the first sentence. Applicant has amended the Specification to correct this error. Reconsideration and removal of the objection is requested.

The Examiner has also objected to the use of the trademark "ISCOM" on page 33, line 17 of the Application. The Examiner notes that each letter of the trademark must be capitalized and accompanied by the generic terminology. Please note that the generic definition of this trademark already appears in the Specification on page 33 at line 17 and at lines 22-24 (ISCOM is an immunostimulating complex matrix consisting of (optionally fractionated) saponins (triterpenoids) from *Quillaja saponaria*, cholesterol, and phospholipid). Applicant, therefore, believes that the trademark has been properly referred to in the Specification and no corrections are needed. Accordingly, reconsideration and removal of the objection is respectfully requested.

Finally, the Examiner has objected to the Specification for failing to provide "proper antecedent basis for the claimed subject matter". Specifically, the Examiner asked Applicant to identify the written support for claim 23 wherein the GDF-8 polypeptide is contained in a virtual lymph node device. The term "virtual lymph node (VLN) device" is already described on page 35, lines 1-20 of the Specification. As such, no amendment to the Specification is needed. Reconsideration and removal of the objection is requested.

6. Rejections under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 2-7, 9-11, 23 and 55. Applicant has cancelled claim 2 thereby obviating the rejection. Claim 4 was rejected for the use of the phrase "suitable chemical groups". Applicant has deleted the word "suitable" thereby obviating the rejection. Claim 23 was rejected because the metes and bounds of the term "virtual lymph node device" were unclear. Applicant believes that a person of ordinary skill in the art could determine the meaning of this term by reference to the Specification. As noted above, this term is described in the Specification on page 35. Finally, the Examiner rejected claim 55 because claim 1 did not provide antecedent basis support for the term "natural T cell epitope". Applicant has amended claim 55 so that it now depends from claim 59. Claim 59 provides proper antecedent basis for this term. Applicant believes that the foregoing amendments and explanations have overcome all of the indefiniteness rejections raised by the Examiner. Reconsideration and removal of the rejections is respectfully requested.

7. Rejections under 35 U.S.C. §112, first paragraph

7.1 The Examiner's Position

The Examiner has rejected claims 1-7, 9-11, 16-17, 19-23, 29 and 53-56 under 35 U.S.C. §112, first paragraph, because the Specification, while being enabling for a method for in vivo downregulation of GDF-8 comprising administering at least one GDF-8 polypeptide of SEQ ID NO:12, or at least one GDF-8 analogue thereof, wherein GDF-8 is derived from bovine GDF-8 polypeptide and wherein the analogue has been modified so that at least one foreign T helper epitope moiety, wherein said T cell epitope is *Tetanus toxoid* epitope is introduced without a carrier molecule, and wherein the modification is substituted in SEQ ID NO:12, does not reasonably provide enablement for a method of in vivo down-regulation of GDF-8 comprising administering any fragment of GDF-8 polypeptide. The Examiner argues that undue experimentation would be required to practice the full scope of the invention because the

Specification provides insufficient guidance and direction as to how to make and use *any* fragments of GDF-8 polypeptide that can induce the production of antibodies against the GDF-8 polypeptide. The Examiner further argues that the Specification does not indicate which amino acid residue within SEQ ID NO:12 can be deleted or substituted and whether the resulting polypeptide would retain the same function as the polypeptide encoded by SEQ ID NO:12. The Examiner has also cited to a number of references which broadly teach that single amino acid changes in an antigen can abolish antibody antigen binding (Colman et al.); single amino acid substitutions outside the antigenic site on a protein affect antibody binding (Abaza et al.); single amino acid substitution in a common allele ablates binding of a monoclonal antibody (Lederman et al.); and that 90% of antibodies raised against intact proteins do not react with any peptide fragment derived from the parent protein indicating that these antibodies are directed to discontinuous epitopes (Van Regenmortel).

The Examiner has also rejected these claims under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner argues that the Applicant is not in possession of a method for in vivo down-regulation of GDF-8 polypeptide comprising administering any fragment of GDF-8 polypeptide. The Examiner further states that the Specification fails to define any fragments of GDF-8 polypeptide that can be used to induce the production of antibodies against the GDF-8 polypeptide and that there is insufficient guidance regarding what substitutions, deletions, or other modifications can be made to SEQ ID NO:12 without affecting the function of the polypeptide. Applicant respectfully disagrees with and traverses the Examiner's conclusion that the full scope of the claims are not enabled or adequately described by the Specification.

7.2 Applicant's Response

As a preliminary matter, it should be emphasized that the focus of the present invention is not to produce a functional GDF-8 polypeptide. Rather, the goal of the invention is to produce a modified GDF-8 polypeptide which has at least one B-cell epitope by inserting (or creating) at

least one foreign T helper cell epitope in the amino acid sequence. This produces an antigenic molecule capable of inducing an antibody response against the self-GDF-8 polypeptide.

In rejecting the claims for lack of enablement and lack of written description, the Examiner focuses on the alleged lack of teaching regarding the preparation of useful GDF-8 molecules and whether the modifications made to the GDF-8 polypeptide would affect its "function". As noted above, the biological function of the polypeptide is not relevant to the method of the present invention. The question is whether the modified polypeptide is antigenic (*i..e.* whether it will induce the production of antibodies). The references cited by the Examiner merely describe changes in antigenicity observed when single amino acid substitutions are made. All of these references report that *monoclonal* antibodies will not bind certain point-mutated proteins. This is not surprising since a monoclonal antibody recognizes a single antigenic determinant (epitope) in a protein. However, antibodies with specificity for other antigenic determinants are not necessarily, and most probably are not, affected by the relevant point mutation.

Applicant would like to point out that the present invention relies on the preparation of antigenic variants of self-GDF-8 that induce a ***polyclonal*** response. The GDF-8 specific antibodies induced this way are reactive with areas of GDF-8 outside the area where a change has been introduced in the sequence. So, while it may be true that utilizing the present technology may destroy some GDF-8 epitopes, the vast majority of GDF-8 epitopes are preserved. It should also be noted that a single point mutation would not be able to destroy all of the epitopes (linear as well as conformational) in the GFD-8 polypeptide. Accordingly, the modified GDF-8 polypeptides according to the invention will retain their antigenicity and will be able to induce an antibody response.

Furthermore, it should be noted that the present claim language requires that an immune response directed against GDF-8 be induced. The Specification provides many examples of how to modify the GDF-8 polypeptide to achieve this effect. The skilled artisan reading the Specification and using knowledge generally available in the art would be able to prepare and select suitable GDF-8 polypeptide analogues for use in the invention. The only requirement, of

course, being that at least one GDF-8 B-cell epitope must be present in the immunogenic construct. This is discussed on page 18, lines 6-26 of the Specification (*e.g.* at lines 16-17 "x modifications [are] introduced between the preserved B-cell epitopes"). The Specification also clearly teaches how to identify suitable constructs that will be capable of inducing the desired effect (see pages 18-19).

In view of the foregoing remarks, it is clear that a person of ordinary skill in the art would be able to prepare suitable antigenic constructs for use in the invention without engaging in undue experiment. Moreover, it is also clear that the Specification provides adequate written description support for the full scope of the invention. This is because a person of ordinary skill in the art would recognize that the inventors were in possession of the claimed invention as they have described how to modify and screen for suitable antigenic constructs for use in the invention and they would have a reasonable expectation that constructs falling within the scope of the claims would induce an antibody response. Accordingly, Applicant respectfully requests reconsideration and removal of the enablement and written description rejections.

8. Rejections under 35 U.S.C. §102(e) and 35 U.S.C. §103(a)

The Examiner has rejected claims 1-2, 16, 19, 22, 29, 53, 54 and 56 under 35 U.S.C. §102(e) as being anticipated by Barker et al. (US Patent 6,369,201). The Examiner has also rejected claims 1-7, 9, 10, 11, 16, 17, 19, 20, 21, 23 and 55 under 35 U.S.C. §103(a) as being unpatentable over Barker et al. in view of the known facts disclosed in the Specification. Applicant has amended the claim to specify that the at least one foreign T helper cell epitope is introduced within specific regions of the GDF-8 polypeptide sequence. Barker fails to describe or suggest the specific modification described in the claims. As such, Applicant submits that the instant claims are both novel and non-obvious in view of Barker and requests reconsideration and removal of the rejections.

Examination on the merits and favorable action on the claims in accordance with the above are requested.

If the Examiner has any questions concerning this application, he is requested to contact Leonard Svensson (Reg. No.: 30,330) the undersigned at (714) 708-8555 in California.

Pursuant to the provisions of 37 C.F.R. § 1.17 and 1.136(a), Applicant hereby petition for an extension of one (1) months to August 8, 2003, 2003 for the period in which to file a response to the Office Action dated April 8, 2003.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on: Aug 8 2003
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BIRCH, STEWART, KOLASCH & BIRCH, LLP

Susan M. Longworthy
(Signature)

Aug 8, 2003
(Date of Signature)